Spatial Patterns of Fixation-Switch Behavior in Strabismic Monkeys

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Purpose. Patients with strabismus perceptually suppress information from one eye to avoid double vision. Mechanisms of visual suppression likely lead to fixation-switch behavior wherein the subject acquires targets with a specific eye depending on target location in space. The purpose of this study was to investigate spatial patterns of fixation-switch behavior in strabismic monkeys.

Methods. Eye movements were acquired in three exotropic and one esotropic monkey in a binocular viewing saccade task. Spatial patterns of fixation were analyzed by calculating incidence of using either eye to fixate targets presented at various gaze locations.

Results. Broadly, spatial fixation patterns and fixation-switch behavior followed expectations if a portion of the temporal retina was suppressed in exotropia and a portion of the nasal retina was suppressed in esotropia. Fixation-switch occurred for horizontal target locations that were approximately greater than halfway between the lines of sight of the foveating and strabismic eyes. Surprisingly, the border between right eye and left eye fixation zones was not sharply defined and there was a significant extent (>10°) over which the monkeys could acquire a target with either eye.

Conclusions. We propose that spatial fixation patterns in strabismus can be accounted for in a decision framework wherein the oculomotor system has access to retinal error information from each eye and the brain chooses between them to prepare a saccade. For target locations approximately midway between the two foveae, strength of retinal error representations from each eye is almost equal, leading to trial-to-trial variability in choice of fixating eye.

Keywords: eye movements, strabismus, monkeys, visual suppression, visual fixation

Strabismus (ocular misalignment) is most commonly a developmental disorder, affecting 2% to 5% of all children.[1–3] Amblyopia is an associated disorder wherein visual acuity of one or both eyes is reduced. If only one eye is amblyopic, patients will fixate and acquire targets with the normal or nonamblyopic eye. However, if amblyopia is minimal, patients with strabismus develop the ability to fixate targets with either eye and can spontaneously change the eye of fixation depending on the location of the target.[4–7] A saccadic eye movement that results in switch in the fixating eye is an alternating saccade.[8] Alternating saccade (fixation-switch) behavior has been demonstrated in both esotropes and exotropes.[4,5,9]

Fixation-switch is likely driven by visual suppression of specific retinal areas of each eye, although mechanisms are yet undetermined.[4–6] Mechanisms of visual suppression in exotropia (divergent strabismus) and esotropia (convergent strabismus) also are controversial.[10,11] Behavioral studies in human exotropes suggest that temporal hemi-retinae are suppressed.[5,12] Metabolic studies in adult monkeys with exotropia and fixation-switch behavior (alternating fixation) also suggest that portions of temporal retinae in the two eyes are suppressed.[13] Most recently, Economides and colleagues[14] extended our understanding of suppression in exotropia when they showed that the fovea of the deviated eye was not suppressed and that parts of the temporal retina adjacent to the fovea also were not suppressed. Studies of suppression in esotropes show more varied results. Some studies have suggested that esotropes who show alternating cross-fixation might demonstrate suppression of the nasal hemi-retinas of the two eyes.[5,15] Other studies have suggested that patients with an esotropic strabismus develop specific areas of suppression (suppression scotomas) within the nasal hemi-retina rather than complete nasal hemi-retinal suppression.[16] Perhaps some of the confusion regarding suppression in exotropia and esotropia is rooted in the methodology used to detect visual suppression. Visual suppression works best when subjects view binocularly under normal viewing conditions. However, measuring suppression in a laboratory setting usually requires the presentation of different stimuli to the two eyes (dichoptic viewing) that might itself interfere with the suppressive state.

Examining fixation-switch behavior in strabismus is interesting because it is the oculomotor outcome of attempting to acquire and fixate targets in the presence of visual suppression. Therefore, examining spatial patterns of fixation in strabismus may provide insight into the underlying patterns of visual suppression. Additionally, testing is performed without the potential confound of dichoptic stimuli. Studying fixation-switch also provides insight into decision processes regarding how sensation (visual information via the fixating and the deviated eyes) is converted into action (a saccade that either does or does not lead to fixation-switch) in strabismus. Monkeys with strabismus, whose strabismus was induced by either surgical[17] or sensory methods,[8] show fixation-switch

behavior, making them a good model system to understand this unusual visual-oculomotor behavior. In this study, we present data from exotropic and esotropic monkeys and analyze spatial patterns of fixation with the goal of understanding how these relate to underlying patterns of visual suppression. Some of these data have been presented before.[8,18]

Methods

Subjects and Rearing Paradigms

Behavioral data were collected from four strabismic (AZ, GL, SJ, FZ) juvenile rhesus monkeys (*Macaca mulatta*) weighing 6 to 8 kg. Monkey AZ was an esotrope (ET), whereas the others were exotropes (XT). Monkeys were reared at the Yerkes National Primate Research Center, Emory University, Atlanta, Georgia, using an alternate monocular occlusion (AMO) paradigm.[19] In the AMO rearing procedure, soon after birth (within the first 24 hours), an occluding patch (either opaque goggles or dark contact lenses) is placed in front of one eye for a period of 24 hours and thereafter switched to the fellow eye for the next 24 hours. The patch is alternated daily for a period of 4 to 6 months. Therefore, during AMO rearing, binocular vision is severely disrupted during the first few months of life, the critical period during which the monkeys normally develop proper eye alignment, stereovision, and binocular sensitivity in the brain.[20,21] During rearing, the animals were checked every 2 to 3 hours to verify that the occluding lens was in place. Compliance to lens rearing is usually greater than 90%.

Surgical Procedures and Eye Movement Measurements

Following special rearing, the animals were allowed to grow normally until they were approximately 3 to 4 years of age before starting experiments. Sterile surgical procedures carried out under aseptic conditions using isoflurane anesthesia (1.25%–2.5%) were used to stereotaxically implant a head stabilization post. In the same surgery, a scleral search coil was also implanted in one eye using the technique of Judge and colleagues.[22] Later, in a second surgery, a second scleral search coil was implanted in the other eye. All procedures were performed in strict compliance with National Institutes of Health and ARVO guidelines and the protocols were reviewed and approved by the Institutional Animal Care and Use Committees of Emory University and the University of Houston.

Binocular eye position was measured using the magnetic search coil method (Primelec Industries, Regensdorf, Switzerland). Calibration of the eye coil signal was achieved by rewarding the monkey with a small amount of juice or other reward when the animal looked at a 1° target optotype that was rear projected on a tangent screen 60 cm away from the animal. Calibration of each eye was performed independently during monocular viewing.

Experimental Paradigms and Data Analysis

Eye movement data were collected as the strabismic animals performed a saccade task under binocular viewing conditions, during which the target stepped to random horizontal or vertical locations within a ±15° to 25° grid every 3 seconds (5° increments; monkeys SJ and GL were tested within a ±15° grid; monkey AZ was tested within a ±25° grid; monkey FZ was tested within a ±20° grid). For any trial, the starting location of the target was the same as the ending location of the target from the previous trial (i.e., trials did not begin with the target at a straight-ahead position). The animals were rewarded for fixating the target with either eye to ensure that the fixation behavior was not influenced by reward schedule. Binocular eye and target position feedback signals were digitized at 1 KHz with 12-bit precision (AlphaLab; AlphaOmega Engineering, Nazareth, Israel). The analysis of the saccade data was partially automated and carried out using custom software built in MATLAB (Mathworks, Natick, MA). The computer displayed target position, binocular eye position, and eye velocity traces of a single saccade trial on the screen. Velocity and acceleration signals were generated by digital differentiation of the position signal using a central difference algorithm. Position, velocity, and acceleration signals were filtered using software FIR filters (80 points; 0–80 Hz passband), also designed in MATLAB. The investigator viewed the traces and decided whether the saccade trial was to be accepted or rejected. Trials that were rejected were those in which the animal was not fixating before the target step, the saccade did not appear to be directed toward the target, or if the saccade did not occur within 500 ms of target step. Once a decision to accept the trial was made, mean and SD of control eye acceleration before the saccade was calculated over a 100-ms fixation period selected by the user. Saccade onset was automatically determined by the software as the first time point at which eye acceleration was greater than 3 SDs away from the control eye acceleration, and saccade offset was determined as the last time point at which eye deceleration was less than 3 SDs away from the same mean eye acceleration. Although detection of saccade onset and offset was automated, the investigator visually examined the eye movement traces of every trial and had the option of either accepting or changing the computer selection. The investigator also made the determination if the saccade led to fixation-switch, and this information was recorded in the computer along with the saccade parameters.

After data collection and initial analysis of saccade onset and offset, the data were parsed into the four bins depending on saccade type: (1) saccades with the right eye fixating the target before and after target step (RR: no fixation-switch and right eye fixating), (2) saccades with the left eye fixating the target before and after the target step (LL: no fixation-switch and left eye fixating), (3) saccades where the right eye was fixating the target before the target step and left eye was fixating the target after the target step (RL: fixation switched from right eye to left eye), and (4) saccades where the left eye was fixating the target before the target step and right eye was fixating the target after the target step (LR: fixation switched from left eye to right eye). The analysis focused on examining the target spatial locations that led to the occurrence of each of these saccade types.

Results

Properties of Strabismus in the AMO Animals

Saccade data are presented here from three exotropic animals (GL, FZ, SJ) and one esotropic animal (AZ) that all showed fixation-switch behavior during binocular viewing. Strabismus angles ranged from 10° to 40° in the four monkeys (AZ, ~35° ET; GL, ~15° XT; FZ, ~10° XT; SJ, ~10° XT). All monkeys also showed varying levels of associated strabismus properties, such as A/V patterns, dissociated vertical deviation, dissociated horizontal deviation, and latent nystagmus. Although visual acuity was not formally measured, the presence of alternation or fixation-switch suggests that the animals did not have severe amblyopia. See our other publications for details of behavioral eye movement properties of similarly reared strabismic monkeys.[8,23–26] In all, 2054 saccade trials from AZ, 1008 trials from GL, 1000 trials from SJ, and 687 trials from FZ were analyzed.

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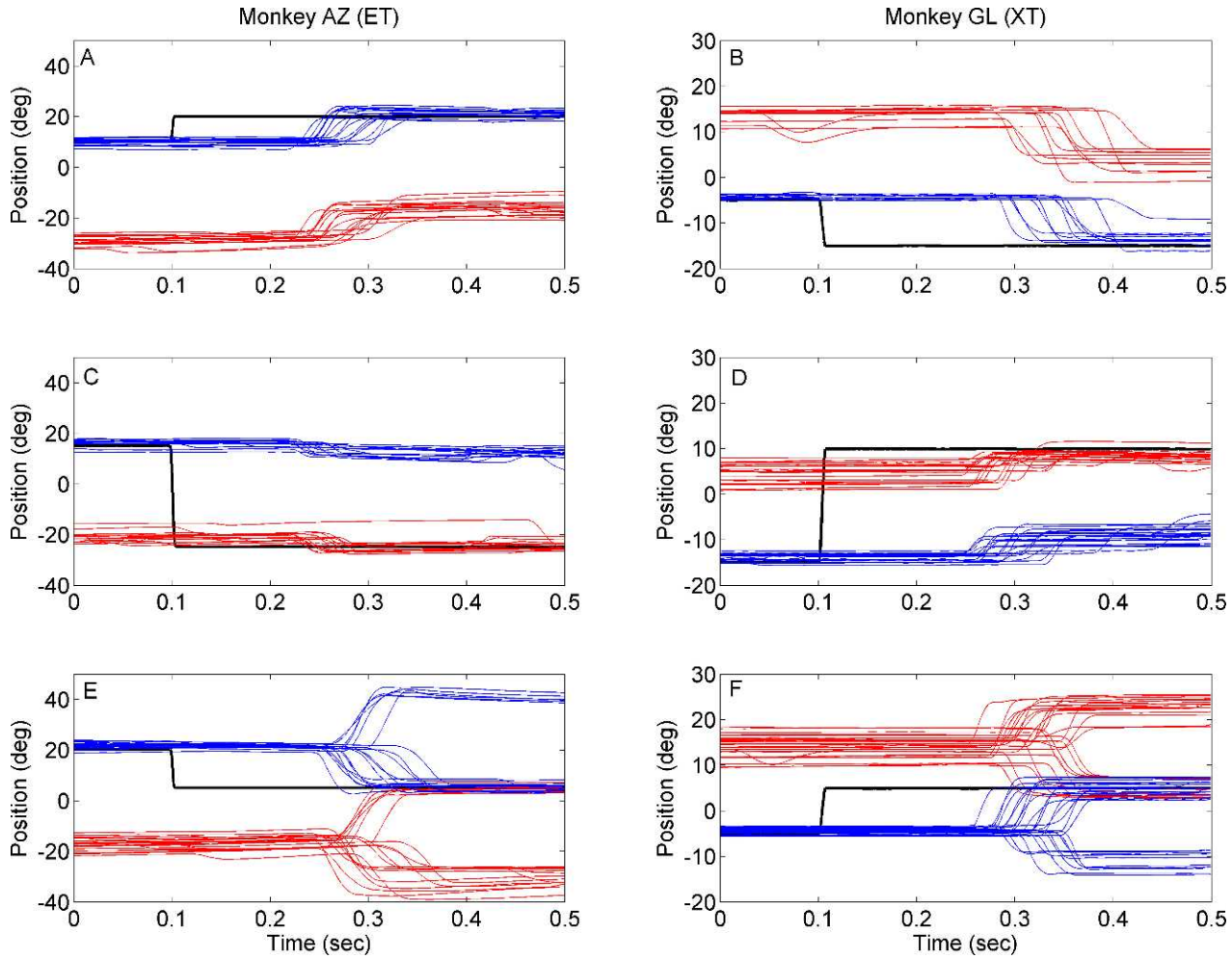

Figure 1. Raw data illustrating fixation-switch behavior during saccades under binocular viewing conditions in esotrope AZ (**A**, **C**, **E**) and exotrope GL (**B**, **D**, **F**). On the *y*-axis is horizontal eye position. Rightward eye positions are positive while leftward eye positions are negative. In each panel, all trials in which the left eye was fixating at target onset are shown. The *red traces* are right eye position, *blue traces* are left eye position, and the *black line* is the target position. (**A**, **B**) illustrate no fixation-switch (LL) trials. (**C**, **D**) illustrate 100% fixation-switch (LR). (**E**, **F**) illustrate fixation-switch on an intermediate percentage of trials.

Fixation-Switch in Esotropic and Exotropic Animals

Figure 1 shows raw eye movement data from the esotropic monkey AZ (Figs. 1A, 1C, 1E) and the exotropic monkey GL (Figs. 1B, 1D, 1F), illustrating the property of fixation-switch in monkeys with strabismus. Each panel shows all saccade trials for a single combination of horizontal target start and end location and with the left eye fixating at target onset. In the esotrope, target steps into the temporal retina of the previously fixating eye (nasal retina of previously nonfixating eye) never results in a fixation-switch (Fig. 1A: 0% fixation-switch; left eye fixates target before target step and after saccade end) and target steps into the temporal retina of the previously nonfixating eye (nasal retina of previously fixating eye) always results in a fixation-switch (Fig. 1C: 100% fixation-switch; left eye fixates target before target step and right eye fixates target after saccade end). An analogous situation is observed in the exotrope, where target steps into the nasal retina of the previously fixating eye (temporal retina of the previously nonfixating eye) never results in a fixation-switch (Fig. 1B: 0% fixation-switch) and target steps into the nasal retina of the previously nonfixating eye (temporal retina of the previously fixating eye) always results in a fixation-switch (Fig. 1D: 100% fixation-switch).

Intermediate target steps that place the target in-between the gaze axes of the two eyes, such as those shown in Figures 1E and 1F, introduce an interesting scenario. In Figure 1E (esotrope), the target steps from a +20° location (left eye fixing the target; right eye is at approximately −20°) to a +5° location, which according to traditional interpretation, places the target on the "suppressed nasal retina" of both eyes. The observation here is that the esotrope introduces a fixation-switch 32% of the time (6/19 trials) and no fixation-switch on the other 68% of the trials (13/19 trials). In Figure 1F (exotrope), the target steps from −5° (left eye fixing the target, right eye is at approximately 10° to approximately 20°) to +5°, which, according to traditional interpretation, is in the "suppressed temporal retina" of both eyes. The observation is that the exotrope introduces a fixation-switch on 37% of trials (10/27 trials) and no fixation-switch on the other 63% of the trials (17/27 trials).

Fixation-Switch Behavior Based on Retinotopic Target Representation

The examples in Figure 1 are from a subset of target start and end locations. Data were collected for a wide range of horizontal and vertical starting and ending locations and we could therefore study the spatial pattern of fixation for the four

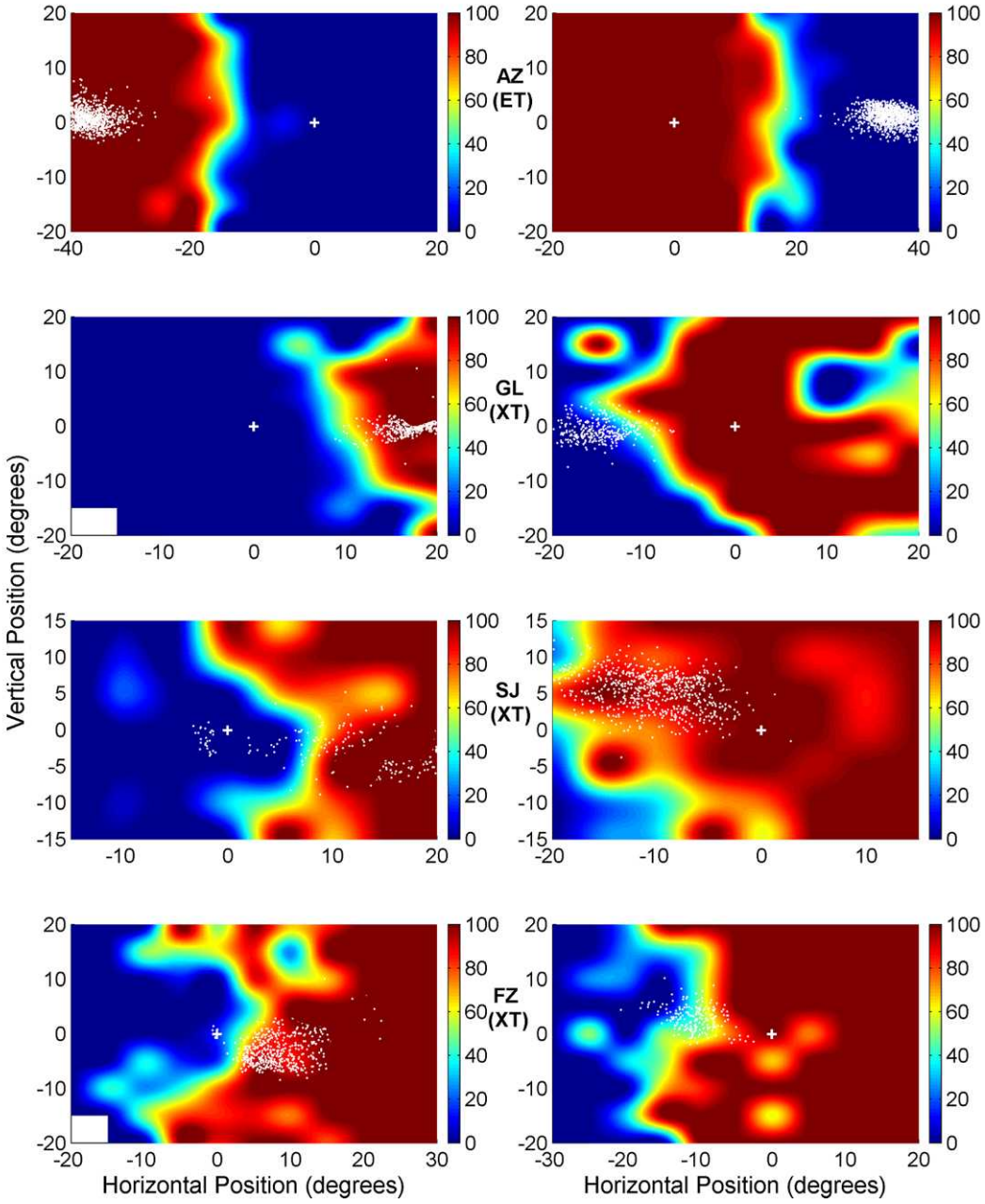

FIGURE 2. Filled surface plots developed from saccade data after target locations are converted to retinotopic coordinates based on previously fixating eye. Panels in the *left column* include trials only wherein the left eye was fixating the target before target step and panels in the *right column* include trials only wherein the right eye was fixating the target before target step. On the *x*-axis is the horizontal position of the target with respect to the fovea of the previously fixating eye, and on the *y*-axis is the vertical position of the target with respect to the fovea of the previously fixating eye. Therefore for left eye fixating (*left column*), positive numbers indicate temporal and inferior retinal locations, and for right eye fixating, positive numbers indicate nasal and inferior retinal locations. Position of the previously fixating eye is the "+" symbol and is located at zero degree. Position of the previously nonfixating eye is shown as *dots* and can be variable from trial to trial.

monkeys in our study. For this analysis, we examined fixation patterns based on retinotopic location of the target with respect to the two eyes (Fig. 2). This is especially relevant when attempting to make a correlation between retinal suppression and fixation-switch. On the *x*-axis in Figure 2 is the horizontal retinotopic position of the target, and on the *y*-axis is the vertical retinotopic position of the target. Plots on the left include only those saccade trials wherein the fixating eye before the target step was the left eye and plots on the right include only those saccade trials wherein the fixating eye before the target step was the right eye. Because the target position data are converted to retinotopic coordinates based on fixating eye before the target step, the position of the previously fixating eye is centered at zero on each panel (shown on plot as a plus symbol). The position of the previously nonfixating eye (i.e., position of nonfixating eye before the target step) is also transformed in this coordinate system and is plotted as dots. The scatter of the dots illustrates that the position of the nonfixating eye before the target step shows significant variability from trial to trial. The color bar shows the percentage of trials in which the right eye acquired the target after the target step. Therefore, red denotes locations

where the right eye acquired the target and blue denotes locations where the left eye acquired the target.

The fundamental finding from the raw data plots in Figure 1 are extended here. For the esotrope, target presentations in the temporal retina of the fixating eye are always acquired by the same eye (i.e., right targets for left eye fixating and left targets for right eye fixating show no fixation-switch). Also, target presentations in the temporal retina of the previously nonfixating eye always led to fixation-switch (target steps to far left locations that are beyond the fovea of the right eye for left eye fixating, and far right targets that are beyond the fovea of left eye for right eye fixating). Additionally clear from this analysis is that target presentations in nasal retina of the previously fixating eye does not always lead to fixation-switch behavior (e.g., nasal targets presented $<20^\circ$ from the fixating eye fovea). Our data therefore show that fixation-switch is not anatomic hemi-retinal. Rather fixation-switch occurs for nasal target presentations that are approximately greater than half the strabismus angle (i.e., roughly midway between the foveal representation of each eye). Also note that the retinotopic location where fixation-switch occurs is not absolute, as shown by the substantial range ($\sim 10^\circ$) over which the colors shift from red to blue. Implications of this observation on the underlying visual suppression patterns are developed later in the discussion section.

The observations in the exotropes can be summarized along the same lines as in the esotrope. Target presentations in the nasal retina of the previously fixating eye are acquired by the same eye (i.e., right targets for right eye fixating and left targets for left eye fixating show no fixation-switch). Also, target presentations in the nasal retina of the previously nonfixating eye led to fixation-switch (target steps to left locations that are beyond the fovea of the left eye for right eye fixating and right targets that are beyond the fovea of right eye for left eye fixating). Target presentations in the temporal retina of the previously fixating eye do not always lead to fixation-switch behavior (i.e., fixation-switch is also not anatomic hemi-retinal in exotropes). Rather, fixation-switch occurs for temporal target presentations that are approximately greater than half the strabismus angle (i.e., roughly midway between the foveal representation of each eye), although this observation is partially obfuscated by the large trial-to-trial variability in the position of the nonfixating eye in many of the plots in the exotropes. Again, the boundary where fixation-switch occurs is not fixed, as shown by the large range over which the colors shift from red to blue. Another observation in both the esotrope and the exotropes was that no pattern for fixation-switch behavior was observed along the vertical plane.

Fixation-Switch Behavior Based on Target Location in Space

Another way of examining the data is to consider fixation-switch as a function of target location in space and not with respect to the fovea, as was done for the previous analysis. Because we were primarily interested in examining the occurrence of fixation-switch for movements along the horizontal plane (naso-temporal plane), the vertical component of the movement was disregarded for this analysis. For every combination of horizontal start and end location of the target, we calculated the incidence of each of the four saccade types (RR, LL, RL, and LR). Figure 3 plots this information in the form of a filled surface plot with target start and end location on the *x*- and *y*-axes, and the color representing the incidence of a specific saccade type. Actual data in these plots are located at 5° increments, and the filled surface plot is obtained by interpolating for in-between locations.

Fundamentally, observations are the same as in Figures 1 and 2. In the esotrope, target presentations in the temporal retina of the fixating eye results in no fixation-switch (right targets for left eye fixating in the "LR plot" and left targets for right eye fixating in the "RL plot"' show no saccade trials). Further, fixation-switch (LR and RL) is evoked for target steps into the temporal retina of the previously nonfixating eye. Similar observations may be made in the exotropes. Target presentations in the nasal retina of the fixating eye result in no fixation-switch (e.g., in monkey GL, left targets for left eye fixating in the "LR plot" and right targets for right eye fixating in the "RL plot" show no saccade trials). Further, fixation-switch (LR and RL) is evoked for target steps into the nasal retina of the previously nonfixating eye.

As a control analysis, we examined the incidence of fixation-switch with respect to the vertical component of the target step instead of the horizontal component. Figure 4 shows these data for all four monkeys. As expected, there was no specific spatial pattern to the fixation behavior in any of the animals for the vertical component of the target step.

Relationship Between Strabismus Angle and Fixation Switch

Strabismic humans and monkeys often show moment-to-moment variations in strabismus angle. This point is illustrated in Figures 1 and 2, as shown by the significant scatter in the positions of the nonfixating eye from trial to trial. It is therefore possible that for final target locations that are approximately midway between the gaze axes of the two eyes, the choice of which eye to use to acquire the target is influenced by the instantaneous retinal error associated with each eye before making the saccade. In other words, perhaps the strategy used is to simply bring the "closer" eye onto the target. We therefore analyzed the relationship between instantaneous retinal error with respect to left and right eyes and the incidence of choosing either eye. We did not find a consistent relationship between these two variables in any monkey, suggesting that instantaneous retinal error was not a determining factor for making a choice to switch fixation or to maintain the previously fixating eye. This finding is illustrated in Figure 5, which plots instantaneous retinal error data from monkeys AZ and GL during right eye fixating or left eye fixating. Open circles indicate trials in which there was a fixation-switch and filled circles indicate trials in which there was no fixation-switch. In each of the four plots, there is significant overlap of the open and filled symbols around the middle of the plot, which shows that either eye could acquire the target even if instantaneous retinal error was larger than that of the fellow eye.

Latency Analysis

In a previous publication,[8] we had hypothesized that for any target step, the animals could theoretically have access to two retinal errors (one from each eye) and the brain had to make a decision on which one to use to generate a saccade. The choice of which retinal error to use to develop a saccade program along with which eye was fixating before the target step would determine the generation of a fixation-switch saccade. Reaction time is a common method to investigate choice behavior. Making a choice between two fairly equally likely events (in the current context, a saccade toward a target located approximately halfway between the gaze axes of the two eyes results in almost equal incidence of right eye or left eye fixation) takes a longer processing time than choosing between two events that have significantly different probabilities of occurrence (such as when making a saccade toward an

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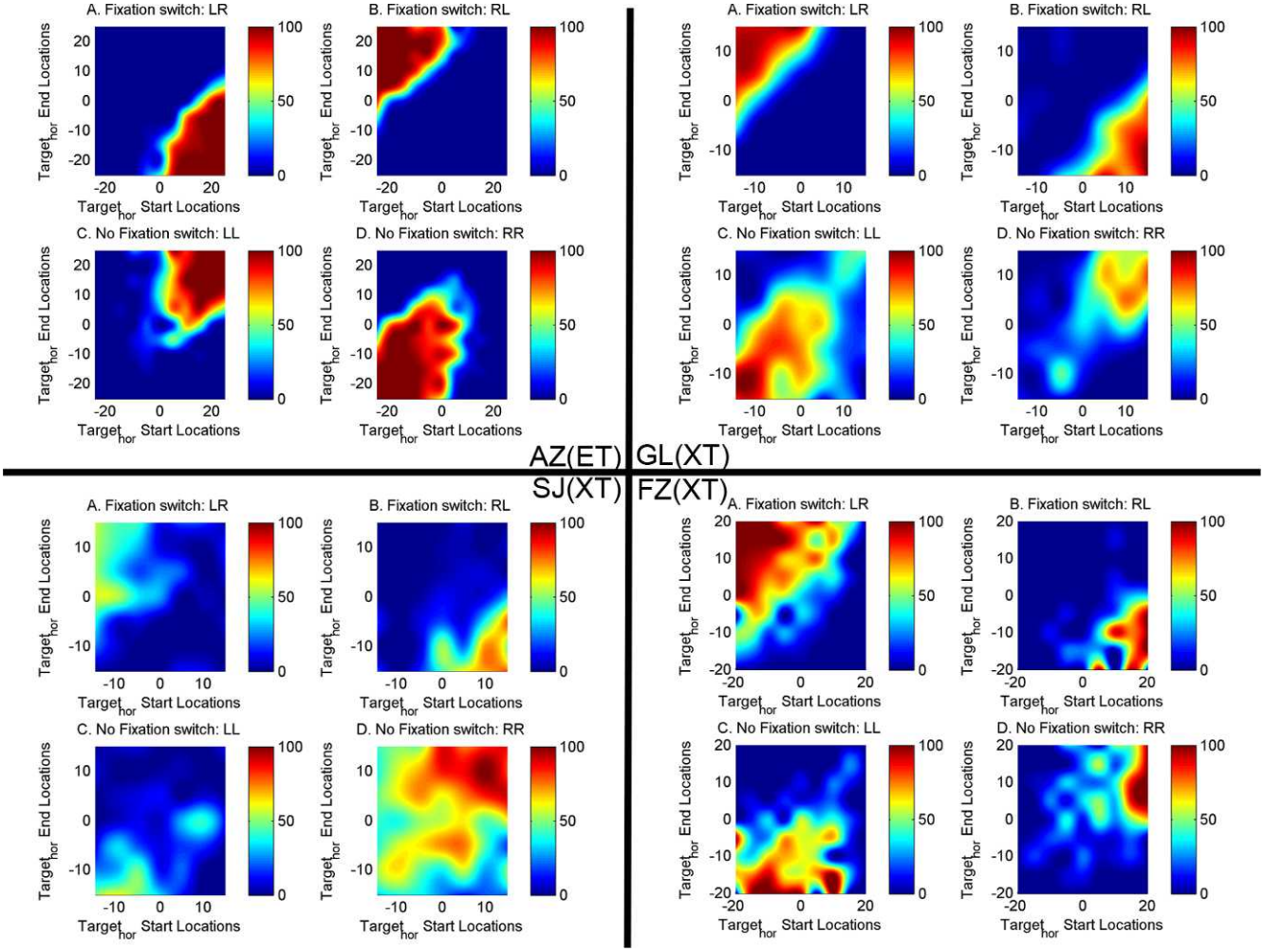

Figure 3. Filled surface plots developed from saccade data in all four animals showing frequency of fixation-switch ([**A**, **B**] in each subplot) or lack thereof ([**C**, **D**] in each subplot) for targets starting and ending at various horizontal locations. On the *x*-axis is the horizontal component of target start location and on the *y*-axis is the horizontal component of target end location. The color scale is the percentage of saccades that were of a specific type (RL, LR, RR, or LL), as indicated on the plot panel title. Plots show that patterns of fixation-switch (RL and LR) or lack thereof (RR and LL) depend on horizontal location of the target in space.

eccentric target that results in almost exclusively right eye or left eye fixation).

To test this hypothesis, we divided the data into three bins: (1) saccade trials for which there was more than 85% incidence of fixating with the previously fixating eye (i.e., "never" switched), (2) saccade trials for which there was more than 85% incidence of fixating with the previously nonfixating eye (i.e., "always" switched), and (3) saccade trials for which there was a 30% to 70% chance of fixation-switch (i.e., sometimes switched). According to our hypothesis, the data in the first two bins were the result of an "easy" choice task (lower latency predicted), whereas the data in the third bin were the outcome of a more "difficult" choice (higher latency predicted). Figure 6 compares the latencies for these three bins for each monkey. Monkey SJ did not have enough trials in bin 2 and so only data in bins 1 and 3 were used for the comparison. Statistical comparisons between bins 1 and 3 (never versus sometimes) resulted in significant differences in three of the four monkeys (AZ: $t[1200] = -6.866$, $P < 0.001$; FZ: $t[334] = 2.095$, $P = 0.037$; GL: $t[630] = -3.715$, $P < 0.001$; SJ: $t[710] = -0.822$, $P = 0.412$). Paradoxically, monkey FZ's saccadic latencies were longer in the "never" switched case than in the "sometimes" switched case. However, his saccadic reaction times were significantly shorter in the "always" switched condition compared with the "sometimes" switched case ($t[220] = -4.494$, $P < 0.001$). The difference between "always" and "sometimes" was also noted for the other monkeys (AZ: $t[856] = 3.242$, $P = 0.001$; GL: $t[382] = 1.989$, $P = 0.047$; no data for SJ). In summary, three monkeys out of four showed significantly longer latency for "sometimes switched" compared with at least one of the "never switched" and "always switched" conditions.

Discussion

In this study, we examined spatial patterns of binocular fixation behavior in esotropic and exotropic strabismic monkeys with the goal of providing insight into how strabismic monkeys and humans might be processing visual information from the two eyes and converting this information into a command for action (i.e., a saccade that either does or does not lead to fixation-switch). Fundamentally, fixation-switch behavior follows what might be expected from patterns of visual suppression in esotropes and exotropes. Thus, exotropes demonstrate fixation-switch for target jumps into the nasal retina of the previously nonfixating eye and esotropes

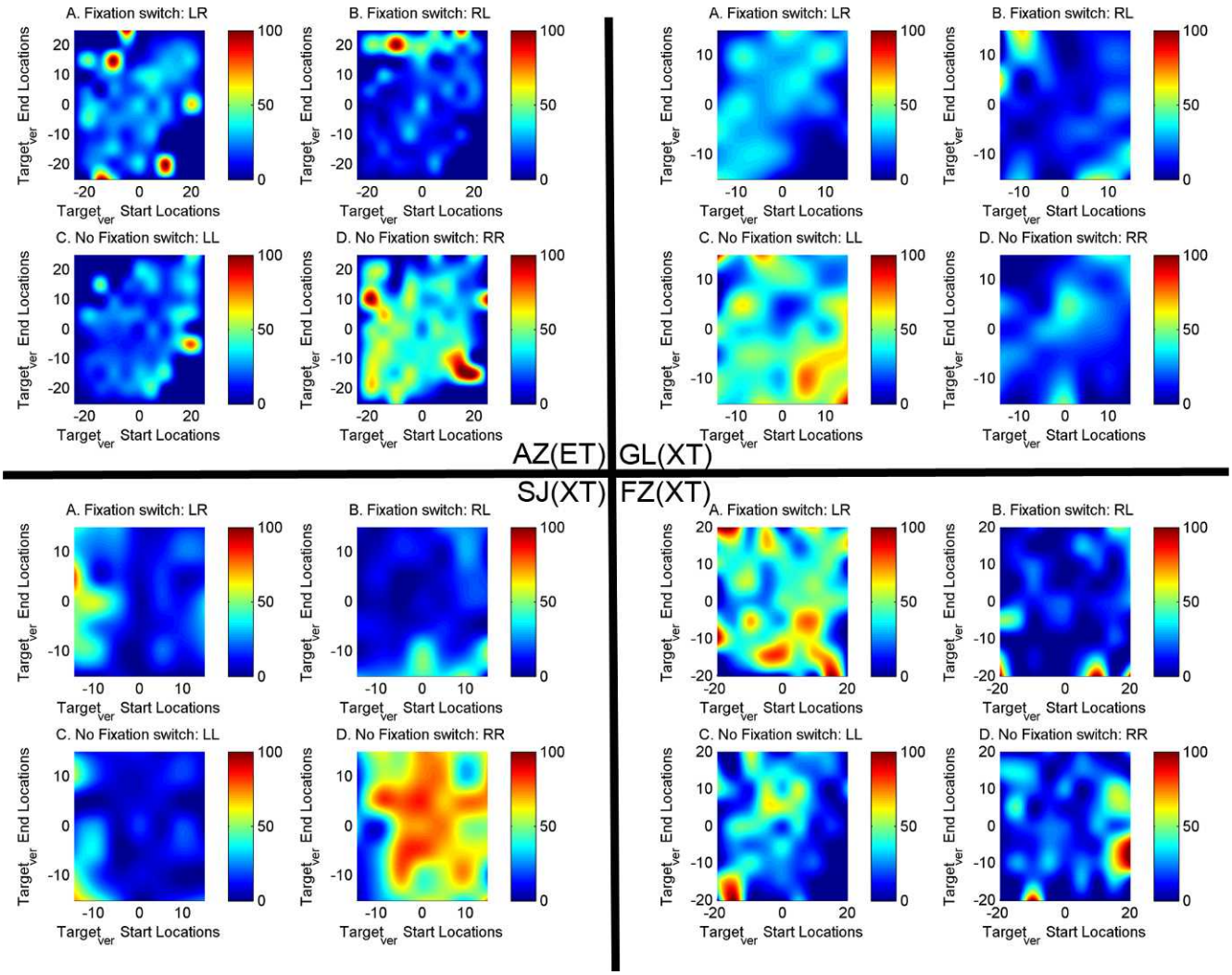

Figure 4. Filled surface plots developed from saccade data in all four animals showing frequency of fixation-switch ([**A**, **B**] in each subplot) or lack thereof ([**C**, **D**] in each subplot) for targets starting and ending at various vertical locations. On the *x*-axis is the vertical component of target start location and on the *y*-axis is the vertical component of target end location. The *color scale* is the percentage of saccades that were of a specific type (RL, LR, RR, or LL), as indicated on *plot panel titles*. Plots show that there is no specific pattern of alternation behavior depending on vertical target location.

demonstrate fixation-switch for target jumps into the temporal retina of the previously nonfixating eye. In esotropia, target jumps into the temporal retina of the previously fixating eye do not result in fixation-switch behavior and in exotropes, target jumps into the nasal retina of the previously fixating eye do not result in fixation-switch behavior.

The most interesting aspect of this study is to try to understand what happens when the target appears in-between the two foveae (i.e., temporal retina of the two eyes in exotropia and nasal retina of the two eyes in esotropia). Early studies did not address this potentially ambiguous situation. Economides and colleagues[14] extended their observations of perception in exotropic strabismic patients to propose a framework wherein the temporal retina close to the fovea in exotropes was not suppressed. This region of unsuppressed temporal retina in the exotrope extended to approximately halfway between the fovea of the two eyes (i.e., half the strabismus angle). Although they did not study esotropes, their argument could presumably also be extended to the esotrope, wherein the nasal retina equivalent to half the strabismus angle would be unsuppressed. The implication of such a suppression strategy would be that target jumps to the temporal retina in the exotrope and the nasal retina of the esotrope would still be acquired by the previously fixating eye as long as the size of the target jump was less than half the strabismus angle. Our data support this framework and also extend it. Figure 2 shows that there is indeed significant tendency toward maintaining the previously fixating eye for target jumps into the temporal retina close to the fovea of the previously fixating eye in the exotrope (nasal retina close to the fovea of previously fixating eye in the esotrope) or toward switching fixation as the target steps to the portion of the temporal retina close to the fovea of the previously nonfixating eye (nasal retina close to the fovea of the previously nonfixating eye in the esotrope). It is also true that the border between the right eye and left fixation is approximately halfway between the fovea of the two eyes (Fig. 2; more clearly seen in the esotrope).

However, the data also clearly show that the border is not sharply defined and there is significant overlap of right eye and left eye fixations in the region midway between the two foveas (shown by the gradual transition of colors between red and blue in Figs. 2 and 3). The perception model of Economides and colleagues,[14] which postulates that the border between the suppressive regions of each retina lies halfway between the

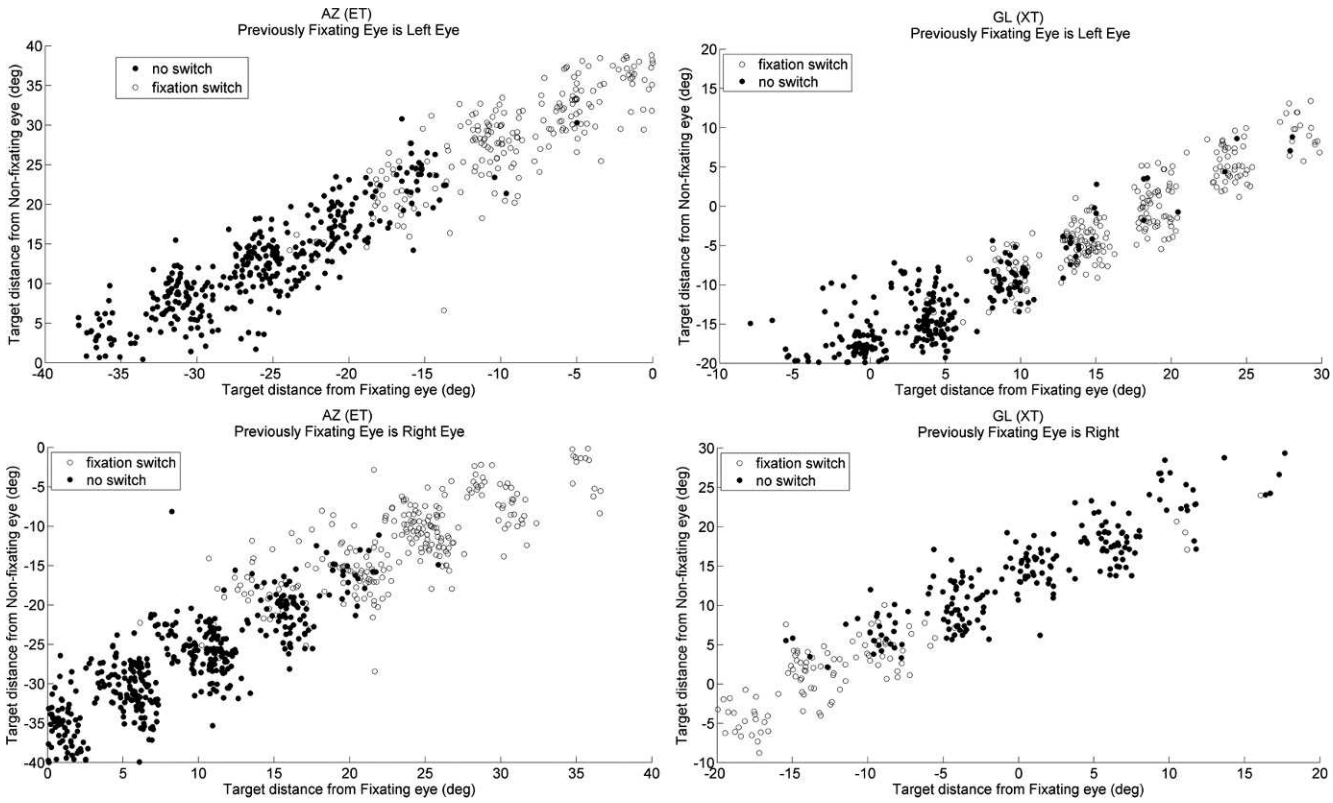

Figure 5. Relationship between fixation-switch and individual trial retinal error with respect to previously fixating and nonfixating eyes in esotrope AZ and exotrope GL. On the *x*-axis is retinal error with respect to previously fixating eye, and on the *y*-axis is retinal error with respect to previously nonfixating eye. *Filled circles* indicate trials wherein no fixation-switch was observed and *open circles* indicate trials wherein fixation-switch was observed. In each plot, there is a region of overlap between the *filled* and *open symbols*, indicating that individual trial retinal error alone does not drive choice of fixating eye.

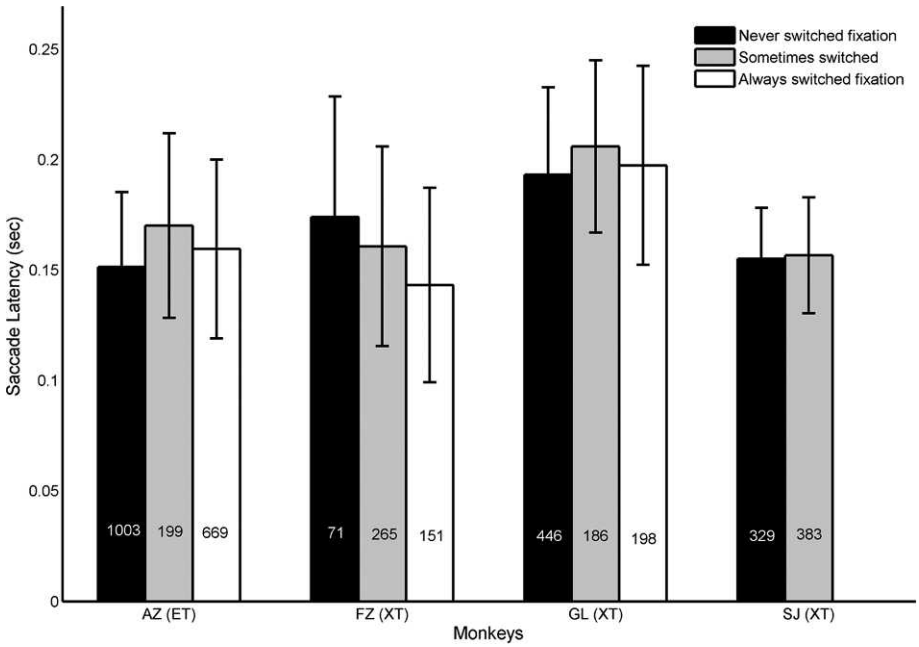

Figure 6. Comparison of saccade latencies for target steps where fixation-switch was "never" observed (*black*), "always" observed (*white*), and "sometimes" observed (*gray*). *Error bars* represent ±1 SD. Numbers in *bars* represent the number of trials in each bin.

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two foveas, does not explain why target jumps to a specific location approximately midway between the two foveas can result in fixations with either eye (Figs. 1E, 1F).

One possible explanation is that, although perceptual visual information is unambiguous (human patients report seeing only one target), the oculomotor system has access to retinal error signals from both eyes. In this scenario, the brain proceeds to make a choice of which retinal error to use when programming the saccade. The strength of the retinal error information from the two eyes would be a fundamental factor in making the decision and varies depending on depth of suppression at that particular retinal location. In the absence of amblyopia, there is likely to be a gradual change in the depth of suppression from peripheral retina to more central retina that is similar in the two eyes. Several studies have suggested that indeed depth of suppression varies across the retina.[16,27–29] In addition, other top-down factors, such as hysteresis (i.e., which eye was used for the previous trials),[30] attentional factors that lead to dynamic priority or salience maps,[31–34] and moment-to-moment neural noise, could influence the strength of the retinal error signal of each eye. The sum of all these influences determines the choice of right eye or left eye fixation. For eccentric targets, the strength of retinal error representation from one of the eyes is significantly stronger (strong suppression of fellow eye) and, therefore, the choice is dominated by this factor. In the border zone (approximately midway between the gaze axes of the two eyes), the strength of the two retinal error signals will be more or less equal and other "noise" factors influence decision-making. Our finding of increased latency for target steps that induce fixation-switch "sometimes" (hard choice influenced by noise factors) versus target steps that "never" or "always" induce fixation-switch (easy choice influenced by retinal error) supports this argument (Fig. 6). Note that our framework for translating suppressed/unsuppressed visual signals into a saccade command that may include a fixation-switch is compatible with the idea of gated accumulation to a threshold model, recently proposed as a framework for target selection and saccade execution in normal humans and monkeys.[35–37] Therefore, verification of our hypothesis may come from neural recording in areas of the brain related to visual salience and target selection, such as the superior colliculus or frontal eye fields.[38–40] One might predict that recordings from visual neurons in the colliculus or frontal eye fields show evidence for multiple retinal errors, whereas motor neurons in these structures show activity correlated only to the saccade that is executed.

A second possibility is that there is dynamic trial-to-trial variability in the extent of each eye's retina that is suppressed or unsuppressed. In other words, there is no overlap of unsuppressed regions (only one retinal error is available to the oculomotor system), but the actual border between the suppressed/unsuppressed regions in right and left eyes varies from trial to trial. One source of variability in the border could be the moment-to-moment variation in strabismus angle due to changes in position of the nonfixating eye. However, when analyzing the data on a trial-by-trial basis, we found no correlation between the eye chosen to acquire the target and the trial-specific retinal error (Fig. 5), suggesting that trial-by-trial variations in strabismus angle was not a determining factor. However, it remains a possibility that there are trial-to-trial variations in the border due to other unknown bottom-up visual and perhaps nonvisual mechanisms.

Economides and colleagues[14] reported that anomalous retinal correspondence (ARC) was a common feature in all the exotropic patients they tested by using an afterimage test. In ARC, the fovea of the fixating eye is matched up with an extrafoveal location (deviated by the strabismus angle), thereby providing a mechanism for maintaining some binocular perception.[1] One advantage of ARC, as pointed out in a review by Serrano-Pedraza and colleagues,[41] is that the fovea of the deviated eye does not need to be suppressed. Herzau[42] suggested that ARC has the most benefit (in terms of providing an usable binocular percept) for targets projected in-between the fovea of the two eyes. Our monkeys were not tested for ARC; however, in our opinion, simply the presence or absence of ARC cannot account for the "fuzzy" border between right and left eye zones. If ARC were a factor, we would expect that the border between right/left eye fixation zones be related to the instantaneous strabismus angle, as the anomalous corresponding points would shift along with the strabismus angle.

The possible presence of ARC underscores the availability of retinal error signals from each eye, setting up the choice paradigm that we hypothesized earlier. Therefore, a more general formulation of our proposed framework is that retinal error signals from each eye are always available (albeit with differing strengths) and are used by the oculomotor system to generate fixation-switch. When these retinal error signals are also used by the visual system to help improve binocular vision or to simply avoid visual confusion, it leads to ARC.

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